Clinical Update

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Intranasal Analgesics for Post-Operative Pain Control

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Introduction

Post-operative pain is a common occurrence following dental surgical procedures.[1] To manage post-operative pain, patients are typically prescribed analgesics, such as a non-steroidal anti-inflammatory drug (NSAID) and an opioid analgesic.

NSAIDs, such as ibuprofen, are a class of analgesics designed to inhibit the cyclooxygenase (COX) enzymes in the arachadonic acid metabolism pathway. By inhibiting the COX enzymes, arachadonic acid will not metabolize into prostaglandins, prostacyclins, and thromboxanes, allowing for these medications to have anti-inflammatory, anti-pyretic, and analgesic properties.[2] However, NSAIDs have been known to cause gastrointestinal bleeding and peptic ulcer formation with long term use.[2]

Opioid analgesics, such as morphine, oxycodone, or hydrocodone, are some of the most potent analgesics available on the market. Opioids centrally reduce the pain sensation by acting primarily on the μ receptor in the brain. However, certain opioids such as fentanyl will also have an effect on the δ and κ receptors.[3] Opioid analgesics are not without side effects. Some of the common side effects associated with opioid analgesics may include sedation, respiratory depression, nausea, vomiting, and constipation.[3]

These medications exist in a variety of formulations, however the oral formulation is most commonly prescribed to dental patients. Medications administered via the oral route are subject to the first pass effect via metabolism in the liver before it is available to the target receptors, which can reduce the bioavailability of the drug.[3] Additionally, the time of onset of pain relief is extended via the oral route compared to intravenous (IV), intramuscular (IM), rectal, sublingual, or transmucosal routes of administration.[3] Anecdotally, patients recovering from dental surgery may be less compliant with oral medications due to the post-operative discomfort they are experiencing. To eliminate some of these problems, intranasal (IN) formulations of these medications have been developed. The IN route is a transmucosal drug delivery method and provides multiple advantages including ease of use, avoidance of the first pass effect, rapid onset of analgesia, and high bioavailability of the medication.[4]

The nasal mucosa is unique in that the blood flow through it is greater per cubic centimeter than that of the muscles, brain, or liver.[4] In addition, anything absorbed through the nasal mucosa has direct access to the central nervous system via the olfactory tract.[3,4] The ability of the medications to readily cross the blood brain barrier via this administration allows for a decreased dose of the pain medication to achieve the desired effect.[4]

Currently, there are two intranasal analgesics available for dental outpatient use for post-operative pain control: intranasal ketorolac and intranasal fentanyl. The purpose of this clinical update is to introduce these two medications, discuss their indications for use, recommended dosages, administration technique, onset, duration of action, and side effects.

Intranasal Ketorolac (Sprix®)

Ketorolac is approved by the Food and Drug Administration (FDA) as an opioid alternative to manage post operative pain for up to five days.[2] Although an NSAID, ketorolac is a potent analgesic with moderate anti-inflammatory effects.[7] Ketorolac can deliver opioid caliber analgesia without the side effects of the opioid or the risk of substance abuse.

Ketorolac is typically administered via the intravenous or intramuscular formulation. Intravenous (IV) or intramuscular (IM) ketorolac has been used since the 1990s as an alternative to opioid analgesia or in combination with opioids as part of a balanced analgesia plan.[2] Administration intravenously or intramuscularly is impractical for outpatient use. In order for patients to benefit from ketorolac in the outpatient setting, the IN formulation has been developed. IN ketorolac, Sprix, is approved by the FDA as an opioid alternative to manage post-operative pain for up to 5 days.

IN ketorolac consists of ketorolac tromethamine in a microcrystalline cellulose carrier.[4] The recommended dose for IN ketorolac is 31.5mg, or one spray in each nostril every 6-8 hours. Each spray contains 15.75mg of ketorolac. The maximum daily dose is 126mg.[2, 5] For elderly patients (patients over the age of 65) and renally impaired patients, the recommended dose 15.75mg every 6-8 hours, or a maximum daily dose of 63mg.[2, 5] IN ketorolac should not be used as a pediatric analgesic.[5]

When administered properly along the nasal mucosa, IN ketorolac is rapidly absorbed into the blood stream.[2,6] Once absorbed through the nasal mucosa, the IN formulation demonstrates a bioavailability of 70% compared to the IM formulation which demonstrated 100% bioavailability.[7] Despite the bioavailability being less than what is seen with IM ketorolac, the IN formulation provides similar blood levels of the drug as the IM formulation.[2] IN ketorolac will reach its peak plasma concentration within 45 minutes following administration.[8] The effects of the rapid absorption and high bioavailability was seen in patients undergoing abdominal or orthopedic surgery. These patients experienced significant pain relief less than an hour after administering the medication. Additionally, the patients noted a significant pain relief lasting up to six hours following their initial dose of IN ketorolac.[8]

Studies in endodontics and oral surgery have shown IN ketorolac to be effective in controlling post-operative pain. In an endodontics study, twenty-two patients in need of root canal therapy were treated with either IN ketorolac or a placebo for post-operative pain. The patients treated with the IN ketorolac had substantial pain relief within 30 minutes following administration of the medication.[8] Following third molar surgery, patients treated with IN ketorolac demonstrated pain relief within 20 minutes of administration of a single dose of the medication. This pain relief was maintained for an additional six to eight hours.[6]

Intranasal Fentanyl (Instanyl®)

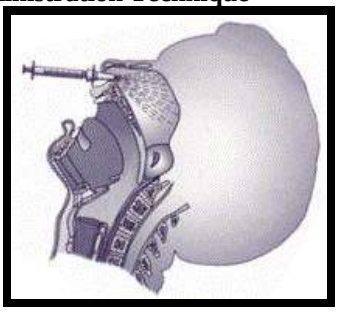
Another intranasal medication available for post-operative pain relief is intranasal fentantyl (Instanyl®). Fentanyl is a lipophilic, synthetic morphine derivative typically used in dentistry for intraoperative discomfort or as an adjunct in intravenous moderate sedation. Fentanyl is used as an analgesic medication for post-operative pain, acute pain treated in emergency departments, wound care pain, and for breakthrough pain in cancer patients.[9]

Fentanyl is processed in many different formulations including intravenous, intramuscular, transmucosal, transdermal, sublingual, rectal, and intranasal. The intranasal route has become a preferred method for outpatient use due to its ability to be quickly absorbed into the blood stream allowing for rapid action on the brain receptors and because it can be self administered by the patient without the need for medical staff intervention.[3,9]

In a review paper, patients prescribed IN fentanyl had comparable pain relief to patients treated with intravenous fentanyl at all dosages. The initial onset of the analgesia for the intranasal medication was slower than the IV route, taking 5 minutes for analgesia, however the duration of action was the same.[3,10] In a study examining post-operative pain control following third molar extractions, IN fentanyl and IV fentanyl given at equivalent doses demonstrated similar results in terms of onset of analgesia and duration of action. In this study patients felt significant pain relief and did not need any rescue medications for approximately an hour with both formulations.[9]

IN fentanyl is available in three different dosages: 50, 100, and 200 µg. One dose is obtained via one spray in one nostril. If a second dose is required, one spray is administered in the other nostril. Doses should be spread out over a ten minute interval. IN fentanyl is recommended for use for up to four breakthrough pain episodes.[10,11]

Intranasal Administration Technique



[12]

The medication is administered similarly to how a patient is administered the FluMist®. The nasal syringe is placed into one nostril gently pushing along the nasal mucosa. The patient must be instructed not to inhale the medication, but just allow it to seep into the nasal mucosa. One spray is administered into one nostril. If a second spray is needed/required, the same procedure is repeated in the other nostril. Depending on the medication being used, the dose can be repeated at home as required.

Side Effects

The most common side effect in all articles discussing both IN ketorolac and IN fentanyl is a minor burning in the nostril following administration. This discomfort is transient and lasts only a few seconds to a minute.[7] Additional common side effects include throat irritation, minor headaches, nausea, and vomiting.[8] IN ketorolac and IN fentanyl should not be prescribed to patients who are advised not to take NSAIDs or opioid analgesics.

Conclusion

The intranasal formulations of these medications allow for a safe non-invasive method to deliver the drug and obtain the desired effects in a rapid manner. The surface area of the nasal mucosa allows for quick absorption of the drug into the blood stream and avoids the first pass effect allowing more allowing more medication to be predictably bio-available. The benefits of less post-operative discomfort, less need for a rescue medication (opioid), and potentially fewer side effects may outweigh the transient side effects such as a burning sensation experienced by the patients. These intranasal formulations provide a way to deliver fast and effective pain control to patients following dental surgery.

Quick Reference Table

	IN Ketorolac[5,13]	IN Fentanyl[11]
Dose	31.5 mg	50, 100, or 200 µg/dose
Rx	One spray in each nostril (15.75mg/nostril) every 6-8 hours for NO MORE THAN 5 DAYS	One spray in one nostril for breakthrough pain every four hours. If second dose is needed, one spray in other nostril. Wait 10 minutes between doses.
Max Daily Dose	126 mg	Recommend use for up to four breakthrough pain episodes/day
Time of onset	30-45 minutes	5 minutes
Half life	6-8 hours	3-4 hours
Side effects	Nasal discomfort, rhinalgia, increased lacrimation, throat irrigation, rhinitis, rash, oligaria, bradycardia, decreased urine output, hypertension, and altered liver enzymes	Common: nasal irritation, nausea, vomiting, throat irritation, headache, dizziness, somnolence, flushing, vertigo Uncommon: epistaxis, constipation, pyrexia, hypotension, respiratory depression

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